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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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MERCK AND CO., INC P O BOX 2000 RAHWAY, NJ 07065-0907			TUCKER, ZACHARY C	
			ART UNIT	PAPER NUMBER
			1624	

DATE MAILED: 06/22/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/614,390	Applicant(s) SU ET AL.	
	Examiner Zachary C. Tucker	Art Unit 1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 24 March 2005.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☐ Claim(s) 1-11 is/are pending in the application.
- 4a) Of the above claim(s) 1 and 5-11 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 2-4 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Election/Restrictions

A Requirement for Restriction in the instant case was mailed 22 February 2005.

Applicant's election of Group I, in the reply filed on 24 March 2005, is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse, though the reply did not state non-traversal of the Requirement (MPEP § 818.03(a)).

Claims 1 and 5-11 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 24 March 2005.

As was explained in the Requirement, when the compound claims are found allowable, a pharmaceutical composition and methods of treatment as set forth in Group II of the Requirement will be rejoined. Upon amendment in Response to this Office action, it is recommended that applicant present claims which depend from the elected compound claims for consideration upon such rejoinder. Claims not commensurate in scope with the allowable compounds will not be rejoined (*i.e.*, claim 1).

A Requirement for an election of species under 35 U.S.C. 121 was also represented in the Office letter mailed 22 February 2005. In response, applicants' counsel has identified the compound of example 56 from the instant specification. This compound is disclosed at page 53, and has the structure depicted on the following page:

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Claim 2 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 8 of allowed application serial no. 10/614,539. Although the conflicting claims are not identical, they are not patentably distinct from each other because instant claim 2 is anticipated by allowed claims 1 and 8 of application number 10/614,539.

To wit:

Claim 8 in the allowed application is drawn to a genus narrower in scope than is instant claim 2. The portion of the structural formula in allowed claim 8 corresponding to "A" in instant claim 2 is fixed as a methylene group; variable group "Y" in instant claim 2 corresponds to a fixed carbonyl in allowed claim 8; the position on the amide nitrogen corresponding to one of R^6 and R^7 of instant claim 2 is fixed as H while the other of R^6 and R^7 is chosen from a small group of $-(CH_2)_n$ -(4-substituted-phenyl) moieties in allowed claim 8, with n' being equal to 0-5, and the 4-substituent on the phenyl ring selected from 4,5-dihydroimidazolyl optionally substituted with one of 4 groups recited; the "E" of instant claim 2 is fixed as a bond in allowed claim 8; R^2 of allowed claim 8, which corresponds to R^5 of instant claim 2 is selected from a small group of substituted phenyls or naphthyls, as opposed to the very large group embraced by the optionally substituted aryl and heteroaryl groups recited in the definition of R^5 of instant claim 2; the positions corresponding to R^{10} , R^{11} and R^{13} in allowed claim 8 are fixed as hydrogen atoms in the allowed claim, as opposed to being selected from scores of possible identities in instant claim 2. Although "Y" in claim 8 of the allowed application is $-SO_2-$, $-CO-$ or CH_2 as opposed to being only $-SO_2-$ in instant claim 2, the balance of claim 8 in

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the allowed application serves to limit that claim to such a small genus so as to anticipate instant claim 2.

The anticipation test between claims is *prima facie* evidence of Obviousness-Type Double Patenting.

Since claim 8 in the allowed application depends from claim 1 of the allowed application, then the subject matter of the instant claims is also embraced by and therefore is obvious over claim 1 of allowed application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3 and 4 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 3, which is an independent claim, the definition for variables R^9 , R^{10} and R^5 refers back to claim 2. An independent claim cannot refer back to another claim for definitions of claim elements recited therein. The definitions for R^9 , R^{10} and R^5 should be incorporated into claim 3.

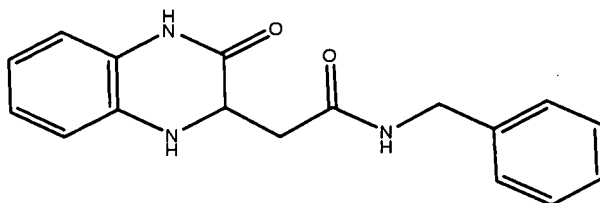
In claim 4, the first two tables of compounds include entries for "Y" which are "-." No explanation as to what significance this has is given. Claim 4 has been examined

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Claim 4 is rejected under 35 U.S.C. 102(b) as being anticipated by Romanenko et al, Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pages 264-266 (1973) or SU 327202, abstract (Burmistrov et al).

The Romanenko et al article is cited in applicants' Information Disclosure Statement filed 18 December 2003. The Burmistrov et al patent is in the Russian language, but an English abstract is provided. An Official translation of Burmistrov et al has been requested from the U.S.P.T.O Translations Branch, and will be provided to applicants with the next Office action. The abstract is being relied upon for the purpose of this rejection.

The compound N-benzyl-1,2,3,4-tetrahydro-3-oxo-quinoxalin-2-yl-acetamide is disclosed in both references – as compound “e” in Romanenko et al on page 244, and in the abstract of Burmistrov et al. The compound has this structure –



and is one according to claim 4, the third table, where R¹ is –CH₂-Ph, R² is H and R⁴ is H. No stereoisomer is designated, so it is implied that the compound is racemic, that is, both R and S configurations are present.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

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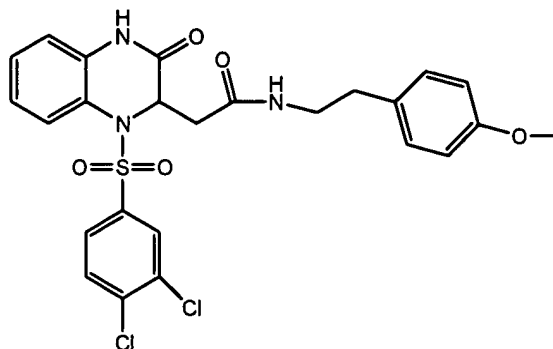
Claims 2 and 3 are rejected under 35 U.S.C. 102(e) as being anticipated by United States Patent Application Publication 2004/0147519 (Grant et al), based on the filing date of provisional application 60/378,206, to which the Grant et al application claims domestic priority, that filing date being 3 May 2002, before the effective filing date of the instant application.

Table I of Grant et al includes at least 3 compounds according to claim 2 and at least one compound according to claim 3.

Compound number 2 is one according to claim 2 wherein A is C₁ alkanediyl (methylene); E is a bond; Y is -SO₂-; R⁷, R⁹, R¹⁰, R¹² and R¹³ are H; R¹¹ is halogen (-chloro); R⁶ is a C₁ alkyl substituted with aryl (benzyl); and R⁵ is aryl substituted with alkyl residues (2,4,6-trimethylphenyl). This compound is not excluded by the provisos at the end of claim 2.

Compound number 13 (page 8 of Grant et al) is one according to claim 2 wherein A is C₁ alkanediyl (methylene); E is a bond; Y is -SO₂-; R⁷, R⁹, R¹⁰, R¹¹, R¹² and R¹³ are H; R⁶ is a C₁ alkyl substituted with aryl, said aryl being substituted with a nitro (4-nitrobenzyl); and R⁵ is aryl substituted with alkyl and halogen residues (4-chloro-2,5-dimethylphenyl). This compound is not excluded by the provisos at the end of claim 2.

Compound number 201 (page 11 of Grant et al) is one according to both claims 2 and 3 wherein A is C₁ alkanediyl (methylene); E is a bond; Y is -SO₂-; R⁷, R⁹, R¹⁰, R¹¹, R¹² and R¹³ are H; R⁶ (R^{6a} in claim 3) is a C₂ alkyl substituted with aryl, said aryl being substituted with a nitro (4-fluorophenethyl); and R⁵ is aryl substituted with alkyl and halogen residues (4-chloro-2,5-dimethylphenyl).



Applicants' counsel indicates in the Response to the Requirement that claims 2-4 read on this elected species.

This species was searched, and no art found, whereupon the search was broadened, eventually to include all of claims 3 and 4. Claim 2, however, has not been fully searched. Prior art anticipating all of claims 2-4, and rendering obvious a compound from claim 4 was found, so the search was stopped. Allowable subject matter is indicated below in the section headed "Allowable Subject Matter."

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

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on the merits with the assumption that “-” stands for a bond. Even if this is true, some definition must be provided in the claim for “-.”

The third table in claim 4 has a column designated “3-Stereo.” The examiner guesses that this column shows the absolute configuration about the 3-position in the compounds. A description of what “3-Stereo” represents should be provided in the claim, as “3-Stereo” is not a term of art. If what the examiner guesses that the term means is correct, there is some ambiguity as to which position on the quinoxaline-one structure applicants consider to be the 3-position. In claim 2, the 3-position in compounds named in the exclusionary proviso at the end of that claim is designated “3-oxo,” which means that applicants consider the carbonyl to be at the 3-position of the quinoxaline-one core structure. If the same holds true for claim 4 compounds, as would be expected, then the 3-position in claim 4 compounds is also the location of a carbonyl. A carbonyl group is not chiral, and therefore “S” and “R” configurations about that position are not possible. Applicants should clarify which position they consider to be the 3-position in claim 4 (last table) compounds. If it is clearly identified, then no ambiguity will be presented, even if claim 2 compounds are named “3-oxo,” because both claims, individually, will be particularly pointed out and distinctly claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over Cunningham and Day, "Synthesis of Benzo[b]-1,4-diazabicyclo[3.2.1]octane" Journal of Organic Chemistry, vol. 38(6), pages 1225-1227 (1973).

At the time the invention was made, the compound according to claim 4 wherein X is (CO)O; R¹ is -CH₃; Y is a bond and R² is H, would have been obvious to one of ordinary skill in the art given the teaching of Cunningham and Day.

Cunningham and Day teach a synthesis of benzo[b]-1,4-diazabicyclo[3.2.1]octane compounds, starting with the ethyl ester of 1,2,3,4-tetrahydro-3-oxo-quinoxalin-2-ylacetic acid. The ester group is reduced with lithium aluminum hydride to the phenethyl alcohol, which is brominated and then subjected to intramolecular cyclization to yield the bridged diazabicyclooctane compound.

The methyl ester of 1,2,3,4-tetrahydro-3-oxo-quinoxalin-2-ylacetic acid would be obvious as a starting material in view of Cunningham and Day's synthesis. The motivation to use the methyl ester instead of ethyl ester would have been to provide a more versatile and adaptable process for making benzo[b]-1,4-diazabicyclo[3.2.1]octane compounds, where a wider variety of starting materials are useable (methyl *and* ethyl esters). Also, Since methanol, which is produced by the

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hydride reduction of a methyl ester, has a lower boiling point than ethanol, the chemist would expect that the methanol by-product would be more easily eliminated by heating than the corresponding situation when reducing the ethyl ester as taught by Cunningham and Day. Clearly, therefore, a methyl ester of 1,2,3,4-tetrahydro-3-oxo-quinoxalin-2-ylacetic acid would be obvious over Cunningham and Day's synthesis wherein the ethyl ester is employed as a starting material.

The methyl ester of 1,2,3,4-tetrahydro-3-oxo-quinoxalin-2-ylacetic acid is a compound according to claim 4, the second table, where X is $-\text{C}(\text{O})\text{O}-$, R^1 is $-\text{CH}_3$, Y is a bond, and R^2 is H.

Abstract of the Disclosure

The specification is objected to because the abstract of the disclosure does not include a generic formula for compounds according to the invention. When the inventive subject matter includes novel compounds, as the title of this application urges, the abstract should at least include a generic structural formula for the novel compounds. Correction is required. See MPEP § 608.01(b).

Allowable Subject Matter

Some of the subject matter of claim 4 is allowable, provided the rejection of that claim under 35 U.S.C. 112, second paragraph and the Obviousness-Type Double Patenting rejection are overcome. This allowable subject matter in claim 4 is all of the compounds in the first table of that claim, all of the compounds in the second table in claim 4 except the first one, and each compound in the third (last) table in claim 4 except the last one specified.

Claim 2 has not been completely searched, due to the nature of Markush practice outlined in MPEP 803.02, and explained above the section headed "Election/Restrictions." Claim 3 could possibly be allowable, should applicants overcome the rejections of that claim, but considerations under 35 U.S.C. 103 may be necessary depending on how applicants amend that claim in response to the rejections under 35 U.S.C. 102(e).

The translation of the Burmistrov et al Soviet patent, when reviewed, may render some species in claim 4 obvious. Specifically, the compounds in the first table where R^1 is either 2-OCH₃-Ph or 3-OCH₃-Ph, Y is a bond, and R^2 and R^4 are H might be obvious in view of the teachings in that reference, since it appears from the abstract that the 4-OCH₃-Ph compound might have been exemplified.

The first named species in the proviso at the end of claim 2 is disclosed in the Romanenko et al reference, cited above in the section headed "Claim Rejections - 35 USC § 102." It is compound Va in that article (page 244); several of the other compounds excluded by the provisos in claim 2 and 3 are disclosed in Table I of United

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States Patent Application Publication 2004/0147519 (Grant et al), also cited above in the rejections under 35 U.S.C. 102.

Upon allowance of the claims in elected Group I (compounds), as set forth in the Requirement for Restriction mailed 22 February 2005, applicants have the right to a rejoinder of method-of-use claims commensurate in scope with the allowable compounds. A claim depending from an allowable compound claim, drawn to a method as recited in withdrawn claims **7** and **8**, so long as "prevention" is struck from the latter claim's preamble, would be deemed allowable under 35 U.S.C. 112, first paragraph.

Close prior art, not relied upon in any claim rejections, is as follows:

US 5,968,951 (Dodey et al) is interesting for its disclosure of bradykinin antagonists which are quinoline ring system and benzenesulfonamide-containing compounds. Dodey et al does not suggest substituting a quinoxaline ring system for the quinoline nucleus in the compounds of that patent.

Varano et al, "Synthesis, Glycine/NMDA and AMPA Binding Activity of Some New 2,5,6-Trioxopyrazino[1,2,3-de]quinoxalines and of Their Restricted Analogs 2,5-Dioxo and 4,5-Dioxoimidazo[1,5,4-de]..." Archive der Pharmazie, vol. 332, pages 201-207 (1999).

This reference teaches a synthesis of fused tricyclic compounds wherein quinoxaline acetic acid esters serve as starting materials (page 202 reaction scheme). The ethyl ester of 8-amino-1,2,3,4-tetrahydro-3-oxo-quinoxalin-2-yl acetic acid and propionic acid are compound "a" and "d" in that reference. The 8-amino group is not permitted in the ester compounds according to instant claim 4, second table.

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Wagh et al, "Reactions of Cyclic Anhydrides, Part VII, Reductive Cyclisation of 2-Nitromaleanilates & 2-Nitrofumarilates, A New Synthesis of 2-Oxo-1,2,3,4-tetrahydroquinoxalines" Indian Journal of Chemistry, vol. 21B, pages 1071-1073 (December 1982).

This reference discloses a series of 2-oxoquinoxalone acetic acid esters. All are ethyl esters except one, which is a methyl ester, but this methyl ester is chloro-substituted at the 6-position, which is not permitted in the first compound in the second table of claim 4. There does not appear to be a motivation to make a methyl ester of compound "6d" in Wagh et al (not 6-substituted), because the authors of Wagh et al were concerned with making those specific compounds reported, that is, the reference is directed at the synthesis of the specific esters "6," unlike the situation with the Cunningham and Day reference, cited above in the section headed "Claim Rejections - 35 USC § 103." Wagh et al does not teach any utility for the compounds "6" disclosed therein, so one of ordinary skill would not be motivated to modify those compounds. Cunningham and Day, unlike Wagh et al, *does* provide a motivation for substituting a methyl ester for an ethyl ester because the methyl ester could provide a better starting material than the ethyl ester.

DE 43 41 663 (Unger et al) discloses endothelin antagonists based on 1,2,3,4-tetrahydroquinoxalin-2-yl acetic acid esters. The compounds are indol-3-ylmethyl substituted at the 4 position of the quinoxaline ring system. Unger et al does not render any of the claimed compounds obvious.

Conclusion

Any inquiry concerning this communication should be directed to Zachary Tucker whose telephone number is (571) 272-0677. The examiner can normally be reached Tuesday-Thursday from 6:00am to 2:30pm, Monday from 6:00am to 1:30pm and Friday from 6:00am to 3:30pm (EST). If Attempts to reach the examiner are unsuccessful, the examiner's supervisor, Mukund Shah, can be reached at (571) 272-0674.

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If, after a 24-hour period, Dr. Shah is unreachable, contact the examiner's acting supervisor, James O. Wilson, at (571) 272-0661.

The fax number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

zt

A handwritten signature in black ink, appearing to be "zt" or a similar stylized name, followed by a horizontal line.